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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/525,797	03/15/2000	Athanasius A Anagnostou	5218-39B	9917

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/525,797	Applicant(s) Anagnostou et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 16, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12-15 and 17-25* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *12-15 and 17-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. The Election filed January 16, 2002 (Paper No. 5) in response to the Office Action of June 19, 2001 (Paper No. 3) is acknowledged and has been entered. Claims 12-15 and 17-25 are pending in the application and are currently under prosecution.

2. Applicant's election without traverse of the species of "simultaneous", claim 23, is acknowledged, however, upon review and reconsideration, the restriction requirement of Paper No. 3 is withdrawn.

Specification

3. The use of the trademarks such as Epogen and Procrit disclosed on page 1, line 22, and page 8 lines 9 and 10 and Taxol disclosed on page 9, line 34 and a plurality of trademarks disclosed on page 10, lines 15-22 of the specification have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Examiner has made an effort to identify informal trademarks but applicant must carefully review the specification to identify and indicate where trademarks may be found. Appropriate correction is required.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

.5. Claims 12-15 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a solid, vascularized tumor with a chemotherapeutic agent, cisplatin, does not reasonably provide enablement for a method of treating a solid vascularized tumor with a chemotherapeutic in combination with erythropoietin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. .

Because of the indefinite nature of the claim language it is assumed for examination purposes that an endothelial-inhibiting amount of erythropoietin is the amount that inhibits endothelial cell proliferation.

The claims are drawn to a method of treating a solid vascularized tumor in a subject in need of such treatment comprising administering an antineoplastic chemotherapeutic agent in conjunction with an endothelial-inhibiting amount of erythropoietin (EPO), wherein the EPO is administered simultaneously, prior to or after administration of the chemotherapeutic agent in an endothelial-inhibiting amount.

(A) The specification exemplifies, in examples 3-4, the effects of 24 hour incubation of EPO and Cisplatin on endothelial cells grown in culture. One cannot

extrapolate the teaching of the specification to the scope of the claims because Example 3 demonstrates a biphasic effect of EPO in that simultaneous treatment of the cultured cells with low doses of EPO together with Cisplatin increases the number of viable cells, compared with Cisplatin control while simultaneous treatment of cultured cells with high doses, greater than 5 U/ml decreases the number of viable cells compared with Cisplatin control. Example 4 demonstrates a similar biphasic effect of EPO treatment in conjunction with Cisplatin wherein the EPO is administered to the cultured cells 2 h after Cisplatin administration. On the other hand, Example 5 demonstrates an inhibitory monophasic effect of EPO when administered prior to the chemotherapeutic agent. The specification does not provide guidance on or exemplification of how to determine the administration protocol for EPO, that is the time before or after administration of the chemotherapeutic Although the specification teaches that an endothelial-inhibiting amount may range from about 750 U/kg to about 2,000 U/kg, given the lack of **in vivo** data, it cannot be determined whether this is the range of EPO required to achieve the claimed affect. These are clearly critical elements in the practice of the instant invention as the time of administration of EPO appears to determine whether biphasic or monophasic affects will be generated. Thus it cannot be predicted from the disclosure whether a particular protocol will result in a cell growth inhibitory or proliferative effect on endothelial cells. The disclosure provides no guidance or exemplifcation of how to determine the time frame, prior to administration of the chemotherapeutic, which is required to produce the monophasic affect.

In addition, a review of related application No. 08/842,700, now US Patent No. 5,922,674 revealed a Declaration filed by Inventor Anagnostou which is relevant to the instant application. The Anagnostou Declaration does not report a biphasic effect of simultaneous administration of EPO and chemotherapeutic agents and thus it is not clear how to interpret the results presented for the tested chemotherapeutic agents. The Anagnostou Declaration appears to repeat the experiments disclosed in Example 3 in that the effects of a range of EPO doses, upon cell growth, were investigated. Clearly, the results of the experiment presented in Example 3, on cultured cells of the same cell type at a dose of 0.15-1.2 U/ml, demonstrate significant increases in the number of viable cells, compared with Cisplatin control. Further, at 2.5 U/ml EPO, Example 3, as shown in Figure 2, reveals a minimal inhibition of cell growth. Interesting, Figure 1 of the Anagnostou Declaration reveals a range of, what appears to be 10-60%, inhibition of endothelial cell growth over the same EPO dosage range of 0.15-2.5 U/ml. The two sets of experiments differ in the final concentration of Cisplatin in the culture media. Experiment 3 uses a final concentration of 1 ug/ml while the data presented in the Anagnostou Declaration uses a final concentration of .7 ug/ml. It is not clear if this suggests that, in order to get a monophasic inhibitory effect, that concentrations of chemotherapeutic agents administered must be determined or whether other differences in the protocol might have led to changes in the combined effects of the chemotherapeutic agent and EPO. The disclosure provides no guidance or exemplification on how to determine the optimal dose of the chemotherapeutic agent that would result in a monophasic inhibitory effect of the combined agents.

Thus, it would not be possible to predict from the data presented that EPO treatment in conjunction with administration of a chemotherapeutic agent would inhibit endothelial cells in a subject treated with a chemotherapeutic agent.

(B) The specification teaches that an embodiment of the invention is a method of treating a solid vascularized tumor by administering an antineoplastic chemotherapeutic agent in conjunction with an endothelial-inhibiting amount of erythropoietin (p. 3, lines 20-26) and the claimed invention appears to be based on data obtained from *in vitro* assays on cell lines which do not even include cancer cell lines (see examples 1-5, pages 13-18). Although it is known that chemotherapeutic agents treat cancer, given the biphasic effects of the EPO, as well as the criticality of chemotherapeutic concentration in the non-cancer cell line tested, one cannot extrapolate the teaching of the specification to the scope of the cliams because there is no way to determine what affect the administration of EPO will have on the efficacy of the chemotherapeutic. The *in vitro* experimental data presented is clearly not drawn to subjects with solid vascularized tumor cells. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly

representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. In addition, *in vivo* administration of EPO and/or Cisplatin may involve different routes, dosages, schedules, etc., and also exposes EPO and/or Cisplatin to complex environments including blood cells and proteins, and also diverse organs such as the liver, lungs, kidney, and spleen, where EPO and/or Cisplatin could be degraded or uptake could remove EPO from the system, thus the fate and activity of the EPO and/or Cisplatin is unpredictable regarding their ability to reach the site of putative action in adequate concentrations to produce the putative cell growth inhibiting effects. Further, it is not clear whether the chemotherapeutic agents will reach the site of putative action in concentrations that will be appropriate for monophasic rather than the biphasic effects of EPO or

that the EPO will reach the site of putative action in concentrations that will be inhibitory rather than stimulatory of cell growth. Further, the *in vitro* example demonstrates effects, after only a 24 hour incubation period wherein the full concentration of the moieties are in full contact with the cells for the entire time which is not the case *in vivo*. Chemotherapy frequently requires protocols that cover weeks or months of therapy and it is not possible to extrapolate the effects of a 24 hour incubation in cultured cells to the effects of *in vivo* EPO administration over a period of weeks or months that could lead to tolerization of the EPO. It is also not possible to predict from the *in vitro* examples whether the well known complications that occur with EPO therapy for anemia such as atherosclerosis and hypertension would occur, thus exacerbating endothelial problems. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, the invention would function as claimed. Finally, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed method would function as claimed.

(C) The specification states that EPO may be administered by any suitable means (p. 11, lines 28-29) in a dosage and timing that will depend on the desired effect (p. 12, lines 6-8) and will be apparent to those skilled in the art (p. 12 line 15-16). One cannot extrapolate the teaching of the specifciation to the scope of the claims because, there is no guidance or exemplification for how to determine dosages or timing of EPO administration that could be used *in vivo* to treat a solid vascularized tumor. Cazzola (Forum Trend Exp. Clin. Med, 1993, 1:344-361, IDS item 9) teaches that the pharmokinetics of recombinant huEPO are different for the two possible route of administration of EPO, iv and sc. After iv injections, plasma concentrations increase sharply and half-life elimination may range from 4-9 hours. After sc injection, there is a slow rise in plasma levels at about 19 hours, that is about 5% of the peak concentration after iv injection of a similar dose, however, half-life is about 21 hours. It has been calculated that with an iv injection of 50 U/kg , 4 times per week the predicted serum EPO concentration is not significantly above basal level during most of the week (p. 351, col 2). It is not clear from the specification how to determine which mode of administration would be most appropriate for treating a vascularized solid tumor, that is (1) whether a short term protocol will enhance endothelial cell growth inhibition or whether the treatment must continue for the duration of the chemotherapy, (2) whether the EPO must be constantly in the system, (3) what dosage would be appropriate *in vivo* since it is apparent from examples 3 and 4 that lower dosages of EPO do not inhibit endothelial cells but increase cell viability and number when associated with Cisplatin treatment. In addition, EPO is endogenously expressed in humans. It is

not clear how the administration of low doses of a substance, already in the system will provide treatment of a solid vascularized tumor.

In view of the above, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

7. Claims 12-15 and 17-25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-15 and 17-25 are indefinite because claim 12 recites the phrase "an endothelial-inhibiting amount". The claims are confusing because it is not clear what is being inhibited, for example, is cell growth being inhibited, or is the production of PGI2, EDRF, thrombomodulin, endothelin GM-CSF or G-CSF being inhibited? Further the term "inhibiting" is a relative term which is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 12-15, 21, 23-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by Platanias et al (J. Clin. Oncol., 1991, 9:2021-2026).

It is noted that claim 21 as written claims EPO administered in an amount of from about 750 Unites per kilogram to about 2,000 Units per kilogram. It is further noted, that the time period for total administration is not defined, either in the specification or the claims. Thus, it is assumed for examination purposes that the amount from 750 Unites per kilogram to about 2,000 Units per kilogram is administered over a five day time period.

The claims are drawn to a method of treating a solid vascularized tumor in a subject in need thereof comprising administering an antineoplastic chemotherapeutic agent in conjunction with an endothelial-inhibiting amount of erythropoietin, wherein the erythropoietin was administered prior to, after or concurrent with the chemotherapeutic agent wherein the chemotherapeutic agent, wherein the erythropoietin is administered in an amount from about 750 Units per kilogram to about 2000 Unitts per kilogram within a week.

Platanias et al teach a method of treating a patient with a solid vascularized tumor comprising administering cisplatin in conjunction with 150-1500 Units per kilogram of EPO over a 5 day period, wherein the EPO is administered during chemotherapy and thus administered prior to, after or concurrent with the chemotherapeutic agent (see p. 2022, col 1 and p. 2025, col 2). The method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering EPO in conjunction with a chemotherapeutic agent within the same endothelial-inhibiting dosage range, thus the claimed method is anticipated

because the method will inherently treat the solid vascularized tumor. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

11. Claims 12-15, 17-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Platanias et al for the reasons previously set forth drawn to the

rejection of claims 12-15, 21, 23-25 and further in view of Markham et al, Drugs, 1995, 49:232-254) and Wood et al., J. Clin. Invest., 1995, 95:1650-1659).

It is noted that claim 21 as written claims EPO administered in an amount of from about 750 Unites per kilogram to about 2,000 Units per kilogram. It is further noted, that the time period for total administration is not defined, either in the specification or the claims. Thus, it is assumed for examination purposes that the amount from 750 Unites per kilogram to about 2,000 Units per kilogram is administered over a five day time period within a week, over a three day period within a week.

The claims are drawn to a method of treating a solid vascularized tumor in a subject in need thereof comprising administering an antineoplastic chemotherapeutic agent, cisplatin, in conjunction with an endothelial-inhibiting amount of erythropoietin administered prior to, after or concurrent with the chemotherapeutic agent wherein the EPO is administered intravenously and wherein the chemotherapeutic agent administered is ciplatin administered intraveneously, wherein the erythropoietin is administered in an amount from about 750 Units per kilogram to about 2000 Unitts per kilogram.

Platanias et al teach as set forth above and further teach that the EPO (p. 2022, col 2) is administered intraveneously but do not teach that the chemotherapeutic agent is cisplatin, do not teach the intravenous administration of cisplatin.

Markham et al teach the treatment of patients with solid tumors undergoing chemotherapy with 300 lU/kg/3 x's per week of EPO (p.248, col 2).

Wood et al teach the conventional administration of cisplatin to cancer patients by intravenous admnistration (p. 1650, col 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the cisplatin of Markham et al for one of the chemotherapeutic agents of Platanias et al because Platanias et al specifically teach the treatment of solid tumors with chemotherapeutic agents and Markham et al teach the treatment of solid tumors with cisplatin, a therapeutic agent. One would have a reasonable expectation of success for substituting the cisplatin of Markham et al for the chemotherapeutic agents of Platanias et al because cisplatin is a well known chemotherapeutic agent. Further, it would have been prima facie obvious obvious to one of ordinary skill in the art at the time the invention was made and one would have have motivated to deliver the cisplatin intravenously because Wood et al teach the conventional administration of cisplating to cancer patients by intravenous administration.

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
March 18, 2002